**D. Remarks:**

Upon entry of the present amendments, claims 1-3, 6, and 13-14 are pending in the application. Claim 1 has been amended to more particularly define the claimed invention. Support for claim 1 as amended can be found in the claims as previously presented. Support for the number of transplanted neural stem cells can be found, for example, at page 14, lines 4-5 of the specification ("a density of about 10,000-1,000,000 cells per μl, preferably 25,000-500,000 cells per μl, is preferred for transplantation"); page 15, lines 15-17 ("multiple deposits of cell sphere suspension may be made, for example 500,000 cells per deposit, in the striatum of the brain"); and page 31, lines 22-25 ("each rat received six deposits of a 0.3 μl sphere suspension, equivalent to approximately 500,000 cells, at the following coordinates . . ."). Thus, since the specification contemplates an upper cell density of 1,000,000 cells per μl, and teaches that multiple deposits can be made, for example 6, recitation of $6x10^6$ cells transplanted to a host subject presents no new matter.

Claim 1 has been further amended to distinguish that the first area of the brain contains multiple loci (*i.e.*, coordinates) for receiving cell deposits. Claim 3 has been amended to reflect substitution of the term "locus" with "area". No new matter has been added.

**Priority**

Applicant acknowledges with appreciation that the Examiner recognizes the earliest effective filing date of the instant application as October 20, 1999.

**Specification.**

Applicant also acknowledges with appreciation the Examiner's withdrawal of the objection to the priority claim in the specification.

**Rejection under 35 U.S.C. § 112, ¶ 1.**

**1. The Standard for Enablement**

In determining whether a particular disclosure satisfies the enablement requirement the factors to be considered are set forth in *In re Wands*, 858 F.2d 731, 737; 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). *Wands* makes clear that the examiner's analysis must consider all of the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole (*see id.* at 737, 740; 8 USPQ2d at 1404, 1407), including any rebuttal evidence provided by the applicant in the form of affidavits or references. *See Manual of Patent Examining Procedure* ("MPEP"), § 2164.05.

The Examiner maintains the rejection of claims 1-3, 6 and 13-14 for lack of enablement. Specifically, the Examiner contends that the specification is insufficient to meet the "how to use" requirement of 35 U.S.C. § 112, first paragraph. *See* Office Action, p. 3. The Examiner asserts that there is a sole utility asserted for the claimed invention; namely, the production of a therapeutic effect or benefit in an animal. According to the Examiner, the specification does not sufficiently teach how to use the methods of the invention to produce such a therapeutic benefit or effect. *See* Office Action, p. 3. However, the Examiner does not provide any evidence to support this contention.

Neither the MPEP nor case law support the Examiner's requirement for a therapeutic benefit to meet the statutory enablement standard.[1] Here the *Wands* factors are met, and that is all that is required for enablement. A plain reading of the instant specification shows that it contains a detailed disclosure commensurate in scope with the protection sought by the claims as amended. As demonstrated below, the specification and Examples, taken as a whole, teach those of ordinary skill in the art how to use the claimed methods.

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1 Although the pending claims do not recite that a therapeutic benefit be achieved, the Examiner has interpreted the claims not only to require a therapeutic benefit but apparently to mean complete graft survivial and reinnervation of host brain tissue. This is error. *In re Cortright*, 165 F.3d 1353; 49 USPQ2d 1464 (Fed. Cir. 1999) makes clear that the interpretation of the claims by the PTO must be consistent with the interpretation that those skilled in the art would reach. In *Cortright*, the Court held that the PTO improperly construed the phrase "restore hair growth" to mean "returning the user's hair to its original state". *See Cortright*, 165 F.3d at 1359. The court noted that the PTO's construction was inconsistent with Cortright's disclosure of partial hair re-growth and with what one of ordinary skill in the art would construe the phrase to mean. Accordingly, the court overturned the PTO's enablement rejection. The enablement rejection should be withdrawn here too.

**2. The Teachings of the Specification**

The specification and evidence of record demonstrate that the ordinarily skilled artisan could discern an appropriate method of use without undue experimentation. Accordingly, one of ordinary skill in the art would be able to routinely use the methods described in the application to induce migration of transplanted neural stem cells via infusion of a mitogenic growth factor. For example, claim 1 as amended herein is directed to a method to transplant at least about $1x10^6$ neural stem cells that are capable of differentiating into neurons, oligodendrocytes, or astrocytes. In this method, at least $1x10^6$ neural stem cells are transplanted to multiple sites of a first area of the brain of a living host. A mitogenic growth factor is then infused at a second area of the brain, causing the undifferentiated neural stem cells to migrate *in vivo* from the deposit sites of the first area toward the second area of the host's brain. The cells retain their responsiveness to the mitogenic growth factor *in vivo*, as well as the ability to differentiate into neurons, oligodendrocytes, or astrocytes. Support for this method is found throughout the specification (*see* specification pages 14-16), and particularly within Example 15 (*See, e.g.*, Specification, page 31, line 23 through page 32, line 3; page 35, line 24 through page 36 line 2; page 37, lines 1-9; and page 41, lines 11-12.)

Furthermore, as indicated by the specification, *in vivo* regulation of neural stem cells transplanted into the brain guides cell migration and/or differentiation, increases graft survival and promotes reinnervation of host tissue, and promotes associated behavioral recovery, enhances the effectiveness of neural stem cell transplantation to serve as a restorative therapy for treating neurodegenerative diseases (*see* Specification, page 41, lines 12-17). Applicant asserts that such a result is indicative of a therapeutic benefit or effect of the claimed invention.

Thus, the specification considered as a whole sets forth how to use the claimed invention in a manner commensurate in scope with the protection sought by the claims. There is ample intrinsic evidence of record that demonstrates how to transplant specific cells (*e.g.*, neural stem cells, as recited in the claims) into the brain of a living host subject and that are known to have the ability to migrate and differentiate, thereby increasing graft survival and enhancing the effectiveness of the transplantation (*See, e.g.*, Specification, page 6, line 24 through page 7, line 7; and Examples 9 and 15).

The instant specification teaches transplanting neural stem cells at a density of 10,000 – 1,000,000 to the brain of a subject under anesthesia by stereotaxic surgery (*See* Specification at page 14, line 4-5; and p. 14, line 23 through page 16, line 16; page 25, lines 20-23). In addition, the specification teaches that the cells can be injected into multiple sites of the brain, including the striatum of the brain, parenchymal sites of the CNS, and intrathecal sites of the CNS (*See* Specification at page 14, line 23 through page 16, line 16; page 25, lines 20-23). The cells can be derived from any suitable tissue source, such as mammalian embryonic tissue (*see* page 15, line 5) and can be cultured in a suspension culture or an adherent culture prior to transplantation (*See* Specification, page 7, lines 5-7; and page 15, lines 4-6). Furthermore, the specification teaches the placement of an infusion cannulae by which to deliver the growth factor within the host in the lateral ventricle (*See* Specification at page 14, line 24-26).

The specification also provides guidance as to the amount of growth factor to be infused. For example, the specification teaches that the total dose required to induce migration and proliferation of transplanted cells will vary from subject to subject, but may be, for example, about 400 ng/day of EGF infused (*See* Specification at page 15, line 22).

Finally, the specification teaches that the infused growth factor regulates the implanted neural stem cells by inducing their migration toward the source of the infused growth factor and that the newly generated cells mass subsequently differentiate into neurons, astrocytes, and oligodendrocytes (*See* Specification, page 15, line 26 through page 16, line 16).

**3. Working Examples**

Also consistent with *Wands*, Applicant has provided several working examples (*e.g.*, Examples 8, 9, and 15), which, taken together, illustrate the methods of the claimed invention so that one of ordinary skill in the art could practice the claimed invention without undue experimentation. The specification describes the procedures for transplanting neural stem cells (*See* Examples 8, 9, and 15). Moreover, several of the working examples demonstrate the responsiveness of the transplanted cells to an EGF infusion (*See* Example 15). In fact, the Examples note that "[m]inimal migration was demonstrated in the adult CNS in the absence of EGF." (*See* Specification, page 26, lines 13-15; *see also* page 33, line 19 through page 34, line 21 and page 35, lines 19 through page 37, line 9). Likewise, the results presented in Example 15

"indicate that neural growth factor infusion can stimulate murine progenitor cells *in vivo*, after transplantation into the adult rat brain" (*See* Specification, page 41, lines 11-12).

For instance, Example 15 describes the induction of *in vivo* proliferation and migration of transplanted progenitor cells in the brain. As described in Example 15, Sprague-Dawley rats received six deposits of 0.3 μl sphere suspensions, wherein each suspension contained approximately 500,000 neural stem cells. (*See* Specification, page 31, lines 23-25). "Immediately after transplantation, a steel infusion cannula was placed in position in the ventricle . . . Infusion was over 7 days with either 400 ng/day EGF dissolved in a solution of 0.1% rat serum and 0.01% gentamycine in 0.9% saline or control vehicle without EGF." (*See* Specification, page 31, line 26 through page 32, line 3). Following EGF-infusion, "there was a striking pattern of M2-positive staining outside the graft core only on the side toward the lateral ventricle . . . There was a significant increase in the number of profiles stained with M2, and these were found throughout the parenchyma as far as the ventricular wall itself. In some animals there was an increase in M2 positivity in the SVZ, with many M2-positive profiles densely packed within this area. In addition, many M2-positive profiles within the region between the graft and the SVZ were seen to be oriented towards the lateral ventricle . . . On the side distal to the ventricle, very little M2-positive staining was observed outside the graft core." (*See* Specification, page 35, line 24 through page 36 line 2). Moreover, as demonstrated in Example 15, the transplanted cells continued to proliferate in response to the EGF-infusion. (*See, e.g.*, page 37, lines 1-9).

Thus, Applicant notes that the working examples correlate with the steps recited in the claimed methods, such that the specification is commensurate in scope with the protection sought by the claims. No undue experimentation is required to practice the methods recited by the claims.

**4. Level of Skill in the Art and Quantity of Experimentation**

Furthermore, the state of the prior art was such that administering the neural stem cell and tissue protocols were well known to the ordinarily skilled artisan at the priority date of this case. As is plain from the evidence already of record, multiple scientific publications confirm that

transplantation of neural stem cells can be routinely achieved. [2/] Furthermore, such transplantation results in a therapeutic benefit to the host. Accordingly, one of ordinary skill in the art as of the filing date would know how to actually carry out the steps as recited by the claims of the instant invention given that the art is replete with examples of transplantation of various other tissue or cells into various parts of the brain.

The Examiner maintains that the papers previously submitted by the Applicant do not embrace the claimed invention and/or do not demonstrate the establishment of a therapeutic benefit (*See* Office Action at pp. 4-5). However, Applicant contends that both the specification as well as the evidence of record demonstrate that the ordinarily skilled artisan with this specification in hand could use the claimed invention to transplant undifferentiated neural stem cells *in vivo*, thereby enhancing the effectiveness of the transplanted cells used as a restorative therapy for neurodegenerative diseases. Moreover, one skilled in the art would recognize that these papers demonstrate that the improvement of delivering a mitogenic growth factor according to the claimed methods would also provide a therapeutic benefit to the host.

The Examiner has not provided any evidence that would lead one of ordinary skill in the art to question the objective truth of the Applicant's statements. *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971) makes clear that it is incumbent upon the Patent Office, whenever a rejection for failure to teach how to make and/or use the claimed invention is made, to explain *why* it doubts the truth or accuracy of Applicant's statement, and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *See Marzocchi* 439 F.2d at 224, 169 USPQ at 370. Here, the Examiner has not provided sufficient evidence in support of the rejection.

Rather, the Examiner merely relies on Jackowski (1995) British J. of Neurosurgery 9:303-17 ("Jackowski") to support the enablement rejection. However, reliance on this reference

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2/ *See, e.g.*, Qu et al., Ageing 12:1127-32 (2001); Akiyama et al., Exp. Neurol. 167:27-39 (2001) ("Akiyama"); Kurimoto et al., Neuroscience Letters 306:57-60 (2001); Nishida et al., Investigative Ophthalmology & Visual Science 41:4268-74 (2000); Reubinoff et al., Nature Biotech 19:1134-40 (2001); Mitome et al., Brain 124:2147-61 (2001); Milward et al., J. Neurosci. Res. 50:862-71 (1997) ("Milward"); Zhang et al., Proc. Natl. Acad. Sci. USA 96:4089-94 (1999) ("Zhang"); Brustle et al., Nature Biotechnol. 16:1040-44 (1998) ("Brustle"); Yandava et al., Proc. Natl. Acad. Sci. USA 96:7029-34 (1999) ("Yandava"); Flax et al., Nature Biotechnol., 16:1033-39 (1993); Fricker et al., J. Neurosci. 19:5990-6005 (1999); Aboody et al., Proc. Natl. Acad. Sci. USA 97:12846-51 (2000); Temple et al., Nature 414:112-17 (2001); Pluchino *et al.*, Nature 422:688-94 (2003) ("Pluchino"); Ishibashi et al., J. Neurosci. Res. 78:215-23 (2004) ("Ishibashi"); and Ogawa et al., J. Neurosci. Res. 69:925-33 (2002) ("Ogawa").

fails for reasons of record previously advanced by Applicant (*e.g.*, Response filed Nov. 30, 2004, pgs. 10-11). Furthermore, the Examiner has improperly evaluated Applicant's evidence (*e.g.*, the post-filing references), solely on its knockdown ability. Rebuttal evidence submitted by applicant in response to a rejection of patentability cannot simply be evaluated on its knockdown ability of an earlier decision. *In re Rhinehart*, 531 F.2d 1048, 1052; 189 USPQ 143 (CCPA 1976). Rather, when evidence is submitted in rebuttal, the decision-maker must start over so that the entire path to decision is retracted. *Id.* Facts established by rebuttal evidence must be evaluated along with the facts on which the earlier conclusions were reached, and not against the conclusion itself, such that a new decision will rest upon evaluation of the evidence as a whole. *See id.*; *see also In re Piasecki*, 745 F.2d 1468, 1472-73 (Fed. Cir. 1984); and *Applied Materials, Inc. v. Advanced Semiconductor Materials America, Inc.*, 98 F.3d 1563, 1570 (Fed. Cir. 1996). Section 2164.05 of the MPEP makes clear that a determination of enablement must be based on the evidence as a whole.

As discussed above, the evidence as a whole shows that, with the extensive detail and working examples provided in the specification, and in conjunction with the level of skill and knowledge possessed by one of ordinary skill in the field of tissue and cell transplantation, the ordinarily skilled artisan would have been able to practice the methods recited by the present claims as of the filing date of the application.

Although further development may be necessary to produce a commercially viable embodiment of the claimed invention, the law makes clear that it is not necessary to enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment of the claimed invention in order to comply with 35 U.S.C. § 112, ¶ 1. *See CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338; 68 USPQ2d 1940, 1944 (Fed. Cir. 2003). Furthermore, as established by the numerous post-filing references of record, therapeutic benefit has been achieved using substantially identical methods to those disclosed in the instant application. Accordingly, one skilled in the art would recognize that these papers demonstrate that the improvement of delivering a mitogenic growth factor according to the claimed methods would also provide a therapeutic benefit to the host subject. Moreover, Applicant notes that the United States Patent and Trademark Office has already allowed several patents directed neural stem cells suitable for on-demand implantation *in vivo* wherein the cells migrate from the implantation

site to another anatomic site for integration within the nervous system of the living host. (*See, e.g.*, United States Patent No. 6,528,306; 6,541,255; and 5,958,767).

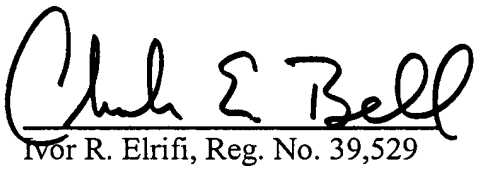
**E. Conclusion:**

For the foregoing amendments and remarks, Applicant respectfully submits that the as-filed specification sufficiently teaches one of ordinary skill in the art how to make and use the invention for its intended purpose, without undue experimentation, and that claim 1-3, 6, and 13-14 are, therefore, allowable. Accordingly, Applicant respectfully requests that the enablement rejection be withdrawn.

Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

The Commissioner is authorized to charge any additional fees that may be due, or to credit any overpayment, to Deposit Account No. 50-0311, Reference 17810-513 (SCI-13).

Respectfully submitted,



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